

Supplemental Material: Materials and Methods

Microarray and gene expression.

Tissue RNA from liver of rats fed HFC ($n = 5$) and HFR ($n = 5$) was extracted using Trizol (Invitrogen) and microarray analysis performed using the Operon Rat Oparray according to the manufacturer's recommendations. RNA integrity was determined with the Agilent 2100 Bioanalyzer and RNA 6000 Nano Kit (Agilent Technologies, Massy, France). A pool of liver RNA from rats fed HFR was used as a common reference. Amplification of mRNA and fluorescent probe synthesis were processed as previously described (Rome et al. 2008). Fragmented fluorescent probes were hybridized with 2X Agilent Hybridization Buffer (Agilent Technologies) on Rattus Norvegicus opArray (Operon Biotechnologies GmbH, Cologne, Germany) in an Agilent oven at 67°C for 17 h, following a dye switch experimental procedure. Microarrays were washed and scanned with a Genepix 4000B scanner (Axon Instruments, Foster City, CA). TIFF images were analyzed using Genepix Pro 6.0 software (Axon Instruments). Signal intensities were log-transformed and normalization was performed by intensity dependant Lowess method. In a first set of analysis, genes with significant difference in expression levels between HFC and HFR were retrieved using the significance analysis of microarray (SAM) procedure with a false discovery rate of 5 % and difference set at 1.2 fold. To compare results from the different experiments, data from each slide were normalized in log-space to have a mean of zero using Cluster 3.0 software. Only spots with signal to noise ratio above 2 and with recorded data on the five slides were selected for further analysis. No dye-effect correction was done in this analysis.

To further characterize the regulated pathways in the liver of rat fed HFC vs. HFR, a second set of analysis was performed. Then the signal intensities of the microarray spots were loaded to R (version 2.8.1), background corrected with a offset of 50 (Silver et al. 2009), lowess normalized within arrays and log transformed using the limma package from BioConductor

(Gentleman et al. 2004). The call for differential expression was done fitting a linear model to each probe. Compared to the SAM analysis described above, we found changes in the relative gene ranking and only 12 genes reaching significance threshold using Benjamini-Hochberg correction. The genes were ordered according to fold-change values and translated to HGNC gene symbols using “getLDS” from the biomaRt package (BioConductor, version 1.16.0) and the Homo Sapiens (NCBI36) and Rattus Norvegicus (RGSC3.4) annotation files. Gene enrichment analysis was performed using the GSEA software (Subramanian et al. 2005) from Broad institute according to the pre-ranked list protocol using the c2.all.v2.5.symbols.gmt curated gene lists. Microarray data are available in the GEO database under number GSE13716.

Quantification of mRNAs using real-time PCR (rtPCR). Validation of the microarray data by measuring the levels of specific mRNA using rtPCR was performed in liver samples from HFC and HFR fed rats ($n = 9$) according to previously published methods (Rome et al. 2008). Total RNA was prepared using Trizol and first-strand cDNAs were synthesized from 500 ng of total RNA in the presence of 100 units of Superscript II (Invitrogen, Eagny, France) using a mixture of random hexamers and oligo (dT) primers (Promega, Charbonnières, France). rtPCR assays were performed using a Rotor-Gene 6000 (Corbett Life-Science). The data were normalized using the expression of beta glucuronidase (*GUSB*) as a reference and expressed as arbitrary unit. The list of the PCR primers is available on request (vidal@sante.univ-lyon1.fr).

Glucose uptake and mRNA expression in 3T3 cells.

Cultured and differentiated 3T3-L1 cells (Petersen et al. 2008) were used to assess insulin-stimulated glucose uptake and mRNA expression of target genes. On day 8 of the differentiation program cells were exposed to vehicle (DMSO) or POP mixtures for 48 hours. Cells were washed first with 200 μ L/well phosphate buffered saline (PBS) pH 7.2 containing

1 mM CaCl₂, and 1 mM MgSO₄, subsequently with 200 µL/well DMEM (1 g/L glucose) and finally incubated in 200 µL/well of the same solution for 2 h at 37 °C. Cells were washed with 200 µL/well Krebs-Ringer-Hepes Buffer (KRHB) pH 7.4, and incubated with 50 µL/well KRHB for 30 min at 37 °C. Fifty µL/well KRHB containing insulin in twice the concentrations indicated were added, and the incubation was continued for 15 min at 37 °C. Glucose uptake was initiated by the addition of 50 µL/well KRHB containing 3.0 mM glucose and 0.25 µL [¹⁴C] 2-deoxy-D-glucose ([¹⁴C] 2-deoxy-D-glucose (100 mCi/L)) yielding a final concentration of 1.0 mM glucose. Cells were incubated for 15 min at 37 °C, and then 50 µL/well 800 mM D-glucose, 50 mM HEPES (pH 7.5), 262 mM NaCl were added. The cells were washed three times in 200 µL/well ice-cold PBS, and lysed in 200µL/well 1 % SDS by shaking for 2 h. Radioactivity in the lysates was determined by scintillation counting. mRNA expression studies were conducted with the following primers (forward and reverse, respectively): *Insig-1*, 5'-GATTCCTCTATATCCGTTCTGGCT and 5'-GGAACACCCATAGCTAACTGTCGT; *Lpin1*, 5'-TGAACACATTGGAGGCCAGGG and 5'-GGCAGGGATTACATGCTGGA.

Exposure of adipocytes with POP mixtures. Adipocytes were treated with several POP mixtures and concentrations of POP compounds within a mixture were chosen according to their relative levels usually found in crude salmon oil. Each mixture was tested at three different concentrations (1 nM, 10 nM, 100 nM, or 1.0 µM) and expressed according to the highest levels of POP compound present within the mixture. At 10 nM, the composition of the mixtures was the following; Organochlorine pesticide mixture: 8.89 nM hexachlorobenzene, 4.88 nM cis-chlordane, 1.39 nM beta-endosulfan, 4.56 nM trans-nonachlor and 10 nM toxaphene. DDT mixture: 0.65 nM op'-DDT, 2.22 nM pp'-DDT, 0.37 nM op'-DDD, 4.96 nM pp'-DDD, 0.76 nM op'-DDE and 10 nM pp'-DDE. PCDD mixture: 10 nM 1,2,3,4,6,7,8-HpCDD. PCDF mixture: 10 nM 2,3,7,8-TCDF and 2.91 nM 2,3,4,7,8-PeCDF. Non-ortho-

substituted PCB mixture: 10 nM CB77, 0.47 nM CB81, 2.94 nM CB126, 0.58 nM CB169. Mono-ortho-substituted PCB mixture: 3.47 nM CB105, 0.23 nM CB114, 10 nM CB118, 0.31 nM CB123, 0.93 nM CB156, 0.23 nM CB157, 0.64 nM CB167, 0.09 nM CB189. PCB mixture: 2.15 nM CB28, 8.36 nM CB52, 7.53 nM CB101, 6.16 nM CB118, 9.91 nM CB138, 10 nM CB153, 1.51 nM CB180. POP mixture was a combination of 10 nM pesticide, 10 nM DDT, 10 nM PCDD, 10 nM PCDF, 10 nM non-ortho-substituted PCB, 10 nM mono-ortho-substituted PCB, and 10 nM PCB mixture. All contaminant compounds were dissolved in DMSO, and the final DMSO concentration in the medium was 0.1%. Contaminant compounds were obtained from Sigma-Aldrich (Leirdal, Norway), LGC Standards (Borås, Sweden) and Dr. Ehrenstorfer (Augsburg, Germany).

References.

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Supplementary materials: Tables and Figures.

Supplemental Material, Table 1. Environmental organic contaminants in high-fat diets.

Persistent organic pollutants (weight/g diet)	High-fat (HF)	High-fat with refined salmon oil (HFR)	High-fat with crude salmon oil (HFC)
Organochlorine pesticides, ng/g			
Alpha-hexachlorocyclohexane	<LOQ	<LOQ	<LOQ
Gamma-hexachlorocyclohexane	<LOQ	<LOQ	<LOQ
Hexachlorobenzene	<LOQ	<LOQ	1.61
Heptachlor	<LOQ	<LOQ	<LOQ
Heptachlor endo-epoxide	<LOQ	<LOQ	<LOQ
Oxychlordane	<LOQ	<LOQ	<LOQ
Trans-chlordane	<LOQ	<LOQ	<LOQ
Cis-chlordane	<LOQ	<LOQ	1.27
Aldrin	<LOQ	<LOQ	<LOQ
Alpha-endosulfan	<LOQ	<LOQ	<LOQ
Beta-endosulfan	<LOQ	<LOQ	0.36
Endosulfan-sulfate	<LOQ	<LOQ	<LOQ
Trans-nonachlor	<LOQ	<LOQ	1.29
Cis-nonachlor	<LOQ	<LOQ	<LOQ
Toxaphene-26	<LOQ	<LOQ	1.48
Toxaphene-32	<LOQ	<LOQ	<LOQ
Toxaphene-50	<LOQ	<LOQ	2.63
Toxaphene-62	<LOQ	<LOQ	1.94
Dichloro-diphenyl-trichloroethanes (DDTs), ng/g			
op'-DDT	<LOQ	ND	0.52
pp'-DDT	0.46	0.49	1.77
op'-DDD	<LOQ	ND	0.27
pp'-DDD	0.13	0.30	3.57
op'-DDE	0.38	0.45	0.53
pp'-DDE	<LOQ	ND	7.16
Polychlorinated dibenzo-p-dioxins (PCDDs), pg/g			
2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)	ND	ND	ND
1,2,3,7,8-Pentachlorodibenzodioxin (1,2,3,7,8-PeCDD)	ND	ND	<LOQ
1,2,3,4,7,8-Hexachlorodibenzodioxin (1,2,3,4,7,8-HxCDD)	ND	ND	ND
1,2,3,6,7,8-Hexachlorodibenzodioxin (1,2,3,6,7,8-HxCDD)	ND	<LOQ	<LOQ
1,2,3,7,8,9-Hexachlorodibenzodioxin (1,2,3,7,8,9-HxCDD)	ND	ND	ND
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (1,2,3,4,6,7,8-HpCDD)	0.11	0.16	0.25
Octachlorodibenzodioxin (OCDD)	0.92	1.18	1.00
Polychlorinated dibenzofurans (PCDFs), pg/g			
2,3,7,8-Tetrachlorodibenzofuran (2,3,7,8-TCDF)	ND	ND	0.99
1,2,3,7,8-Pentachlorodibenzofuran (1,2,3,7,8-PeCDF)	ND	ND	<LOQ
2,3,4,7,8-Pentachlorodibenzofuran (2,3,4,7,8-PeCDF)	ND	ND	0.32
1,2,3,4,7,8-Hexachlorodibenzofuran (1,2,3,4,7,8-HxCDF)	ND	ND	<LOQ
1,2,3,6,7,8-Hexachlorodibenzofuran (1,2,3,6,7,8-HxCDF)	ND	ND	<LOQ
1,2,3,7,8,9-Hexachlorodibenzofuran (1,2,3,7,8,9-HxCDF)	ND	ND	ND
2,3,4,6,7,8-Hexachlorodibenzofuran (2,3,4,6,7,8-HxCDF)	ND	ND	<LOQ
1,2,3,4,6,7,8-Heptachlorodibenzofuran (1,2,3,4,6,7,8-HpCDF)	<LOQ	ND	<LOQ
1,2,3,4,7,8,9-Heptachlorodibenzofuran (1,2,3,4,7,8,9-HpCDF)	ND	ND	<LOQ
Octachlorodibenzofuran (OCDF)	ND	ND	ND
Non-ortho-substituted PCBs, pg/g			
3,3',4,4'- Tetrachlorobiphenyl (CB-77)	0.83	1.20	23.70
3,4,4',5- Tetrachlorobiphenyl (CB-81)	<LOQ	<LOQ	0.90
3,3',4,4',5- Pentachlorobiphenyl (CB-126)	<LOQ	0.40	7.78

3,3',4,4',5,5'- Hexachlorobiphenyl (CB-169)	<LOQ	<LOQ	1.70
Mono-ortho-substituted PCBs, pg/g			
2,3,3',4,4'- Pentachlorobiphenyl (CB-105)	<LOQ	9.43	455.99
2,3,4,4',5- Pentachlorobiphenyl (CB 114)	ND	ND	29.81
2,3',4,4',5- Pentachlorobiphenyl (CB-118)	4.30	16.64	1314.35
2',3,4,4',5- Pentachlorobiphenyl (CB-123)	ND	<LOQ	41.17
2,3,3',4,4',5- Hexachlorobiphenyl (CB-156)	ND	26.89	135.18
2,3,3',4,4',5'- Hexachlorobiphenyl (CB-157)	<LOQ	7.36	37.46
2,3',4,4',5,5'- Hexachlorobiphenyl (CB-167)	<LOQ	15.06	92.57
2,3,3',4,4',5,5'- Heptachlorobiphenyl (CB-189)	<LOQ	5.86	14.04
Polychlorinated biphenyls (PCBs), ng/g			
2,4,4'-Trichlorobiphenyl (CB-28)	0.07	0.12	0.36
2,2',5,5'-Tetrachlorobiphenyl (CB-52)	0.16	0.36	1.59
2,2',4,5,5'-Pentachlorobiphenyl (CB-101)	<LOQ	<LOQ	1.60
2,3',4,4',5-Pentachlorobiphenyl (CB-118)	0.004	0.02	1.31
2,2',3,4,4',5'-Hexachlorobiphenyl (CB-138)	<LOQ	0.14	2.33
2,2',4,4',5,5'-Hexachlorobiphenyl (CB-153)	<LOQ	<LOQ	2.35
2,2',3,4,4',5,5'-Heptachlorobiphenyl (CB-180)	<LOQ	0.17	0.39

Supplemental Material, Table 2. Fatty acid composition of high-fat diets.

Fatty acids (mg/g diet)	High-fat (HF)	High-fat with refined salmon oil (HFR)	High-fat with crude salmon oil (HFC)
Saturated			
C14:0	2.8	9.3	9.6
C15:0	0.0	0.6	0.6
C16:0	64.3	62.1	61.5
C17:0	0.9	1.1	1.1
C18:0	28.3	28.4	27.6
C20:0	1.2	0.7	0.6
C22:0	0.0	0.0	0.0
C24:0	0.0	0.0	0.0
Sum	97.5	102.2	101.0
Monounsaturated			
C16:1n-7	4.2	12.0	11.5
C18:1n-7	5.8	10.7	10.0
C20:1n-7	0.0	0.3	0.2
C14:1n-9	0.0	0.0	0.0
C16:1n-9	0.8	1.1	1.1
C18:1n-9	126.0	123.1	122.1
C20:1n-9	1.8	11.0	9.9
C22:1n-9	0.0	1.3	1.3
C24:1n-9	0.0	1.0	1.1
C18:1n-11	0.0	0.7	0.5
C20:1n-11	0.0	1.1	0.9
C22:1n-11	0.0	7.8	7.7
Sum	138.6	170.0	166.3
Polyunsaturated			
C18:2n-6	128.5	40.7	41.1
C20:2n-6	1.0	2.1	2.4
C20:3n-6	0.0	0.3	0.4
C20:4n-6	0.2	1.2	1.3
C16:2n-4	0.3	0.7	0.8
C16:3n-3	0.0	0.4	0.5
C16:4n-3	0.5	0.6	0.7
C18:3n-3	2.6	7.5	7.7
C18:4n-3	0.0	2.0	1.9
C20:3n-3	0.0	0.5	0.6
C20:4n-3	0.0	2.0	2.3
C20:5n-3	0.0	10.1	10.1
C22:5n-3	0.0	4.7	5.4
C22:6n-3	0.0	13.0	13.6
Sum n-6	129.7	44.3	45.3
Sum n-3	3.1	40.7	42.8
n6/n3	42.0	1.1	1.1

Supplemental Material, Table 3. List of the differentially expressed genes in liver of rats fed HFC compared to HFR.

Symbol	LLID	Name/Description	Fold change	SEM	Cytoband	Ensembl Gene_id
Metabolism						
<i>Lipid metabolism</i>						
<i>Apolipoprotein B-100 precursor</i>	54225	Apolipoprotein B-100 precursor	1.41	0.12	6q14	ENSRNOG00000005542
<i>Peroxisomal carnitine O-octanoyltransferase</i>	83842	Peroxisomal carnitine O-octanoyltransferase	1.34	0.06	4q12	ENSRNOG00000006779
<i>ATP-binding cassette, sub-family G (WHITE), member 3</i>	498327	ATP-binding cassette, sub-family G (WHITE), member 3	1.28	0.09	14p22	ENSRNOG00000031458
<i>Acyl-CoA thioesterase 4</i>	681337	Acyl-CoA thioesterase 4	1.26	0.08	6q31	ENSRNOG00000033887
<i>Aldehyde dehydrogenase 8 family, member A1</i>	685750	Aldehyde dehydrogenase 8 family, member A1	1.26	0.08	1p12	ENSRNOG00000014907
<i>Apolipoprotein O-like</i>	317191	Apolipoprotein O-like	1.22	0.04	Xq31	ENSRNOG00000004512
<i>3-ketodihydrophosphingosine reductase</i>	360833	3-ketodihydrophosphingosine reductase	-1.26	0.05	13p13	ENSRNOG00000002781
<i>Serum amyloid A 4</i>	365245	Serum amyloid A 4	-1.30	0.04	1q22	ENSRNOG00000012232
<i>Phosphatidylcholine:ceramide cholinophosphotransferase 1</i>	353229	Phosphatidylcholine:ceramide cholinophosphotransferase 1	-1.30	0.08	1q52	ENSRNOG00000012536
<i>Patatin-like phospholipase domain-containing protein 2 (Adipose triglyceride lipase)</i>	361676	Patatin-like phospholipase domain-containing protein 2 (Adipose triglyceride lipase)	-1.36	0.08	1q41	ENSRNOG00000018736
<i>Fatty acid desaturase 3</i>	286922	Fatty acid desaturase 3	-1.43	0.09	1q43	ENSRNOG00000020385
<i>Cytosolic acyl coenzyme A thioester hydrolase, inducible</i>	50559	Cytosolic acyl coenzyme A thioester hydrolase, inducible	-1.51	0.20	6q31	ENSRNOG00000028870
<i>2-hydroxyacyl-CoA lyase 1</i>	85255	2-hydroxyacyl-CoA lyase 1	-1.54	0.09	16p16	ENSRNOG00000019630
<i>Fatty acid desaturase 2</i>	83512	Fatty acid desaturase 2	-1.71	0.24	1q43	ENSRNOG00000020440
<i>similar to Insulin-induced gene 1 protein (INSIG-1)</i>	688922	similar to Insulin-induced gene 1 protein (INSIG-1)	-1.80	0.27	4q22	ENSRNOG00000027445
<i>Cytochrome P450 2J3</i>	65210	Cytochrome P450 2J3	-1.90	0.23	5q33	ENSRNOG00000031004
<i>Lipin 1</i>	313977	Lipin 1	-3.63	1.12	6q15	ENSRNOG00000004377
<i>Steroid metabolism</i>						
<i>Aldo-keto reductase family 1, member C1</i>	307092	Aldo-keto reductase family 1, member C1	2.21	0.18	17q12.3	ENSRNOG00000017236
<i>Sulfotransferase family 2A, dehydroepiandrosterone (DHEA)-preferring, member 1</i>	361510	Sulfotransferase family 2A, dehydroepiandrosterone (DHEA)-preferring, member 1	1.69	0.24	1q21	
<i>Similar to 20-alpha-hydroxysteroid dehydrogenase</i>	498789	Similar to 20-alpha-hydroxysteroid dehydrogenase	1.60	0.12	17q12.3	ENSRNOG00000038361
<i>Cytochrome P450, family 3, subfamily a, polypeptide 2</i>	266682	Cytochrome P450, family 3, subfamily a, polypeptide 2	1.37	0.19	12p11	ENSRNOG0000000978
<i>3 beta-hydroxysteroid dehydrogenase/Delta 5->4-isomerase type 1</i>	360348	3 beta-hydroxysteroid dehydrogenase/Delta 5->4-isomerase type 1	1.36	0.13	2q34	ENSRNOG00000019454
<i>3 beta-hydroxysteroid dehydrogenase type 7</i>	246211	3 beta-hydroxysteroid dehydrogenase type 7	1.29	0.09	1q36	ENSRNOG00000019080
<i>Estrogen sulfotransferase</i>	360268	Estrogen sulfotransferase	1.26	0.08	14p21	ENSRNOG00000001957
<i>Hydroxysteroid (17-beta) dehydrogenase 6</i>	286964	Hydroxysteroid (17-beta) dehydrogenase 6	1.22	0.03	7q11	ENSRNOG00000007758
<i>Sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, S. cerevisiae)-like</i>	114100	Sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, S. cerevisiae)-like	1.21	0.06	8q22	ENSRNOG00000008305
<i>Xenobiotic/drug metabolism</i>						
<i>Cytochrome P450 2C70</i>	171518	Cytochrome P450 2C70	1.39	0.07	1q53	ENSRNOG00000021924
<i>Cytochrome P450 2C7</i>	29298	Cytochrome P450 2C7	1.38	0.12	1q53	ENSRNOG00000021405
<i>Catechol O-methyltransferase</i>	24267	Catechol O-methyltransferase	1.36	0.10	11q23	ENSRNOG00000001889
<i>Dimethylaniline monooxygenase [N-oxide-forming] 1</i>	25256	Dimethylaniline monooxygenase [N-oxide-forming] 1	1.35	0.11	13q22	ENSRNOG000000034191
<i>Cytochrome P450, 2C37</i>	29296	Cytochrome P450, 2C37	1.35	0.14	1q52	ENSRNOG00000021405
<i>Aldo-keto reductase family 1, member C-like 2</i>	307091	Aldo-keto reductase family 1, member C-like 2	1.30	0.09	17q12.3	ENSRNOG00000017165
<i>Cytochrome P450 7B1</i>	25429	Cytochrome P450 7B1	1.27	0.07	2q24	ENSRNOG00000009730
<i>Aldehyde dehydrogenase 1 family, member A1</i>	24188	Aldehyde dehydrogenase 1 family, member A1	1.26	0.10	1q51	ENSRNOG00000017619
<i>Similar to Cytochrome P450 2C24</i>	687842	Similar to Cytochrome P450 2C24	-1.37	0.07	1q53	ENSRNOG00000001466
<i>Dimethylaniline monooxygenase 3</i>	84493	Dimethylaniline monooxygenase 3	-1.50	0.17	13q22	ENSRNOG00000003620
<i>Cytochrome P450 3A18</i>	252931	Cytochrome P450 3A18	-1.76	0.26	12p11	ENSRNOG0000000969
<i>Other metabolic pathways</i>						
<i>Similar to ubiquinol-cytochrome c reductase complex 7.2kDa protein isoform a</i>	686947	Similar to ubiquinol-cytochrome c reductase complex 7.2kDa protein isoform a	1.52	0.20	15	ENSRNOG00000009521
<i>Choline/ethanolamine kinase</i>	29367	Choline/ethanolamine kinase	1.29	0.07	7	ENSRNOG00000011404
<i>Phosphoribosylaminoimidazole carboxylase</i>	140946	Phosphoribosylaminoimidazole carboxylase	1.23	0.07	14p11	ENSRNOG0000002101
<i>NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1</i>	363441	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1	-1.20	0.04	Xq11	ENSRNOG00000040005
<i>Aconitate hydratase, mitochondrial precursor</i>	79250	Aconitate hydratase, mitochondrial precursor	-1.24	0.06	7q34	ENSRNOG00000024128
<i>Cystathione beta-synthase</i>	24250	Cystathione beta-synthase	-1.26	0.05	20p12	ENSRNOG00000029528
<i>Phosphoenolpyruvate carboxykinase, cytosolic</i>	362282	Phosphoenolpyruvate carboxykinase, cytosolic	-1.27	0.08	3q42	ENSRNOG00000028616
<i>Debranching enzyme homolog 1 , mRNA</i>	681234	Debranching enzyme homolog 1 , mRNA	-1.32	0.08	8q31	ENSRNOG00000014588
<i>Glycogen synthase 2</i>	25623	Glycogen synthase 2	-1.36	0.10	4q44	ENSRNOG00000012783
<i>Nicotinamide phosphoribosyltransferase</i>	297508	Nicotinamide phosphoribosyltransferase	-1.38	0.09	6q16	ENSRNOG00000009754
<i>Dehydrogenase/reductase (SDR family) member 7</i>	299131	Dehydrogenase/reductase (SDR family) member 7	-1.46	0.13	6q24	ENSRNOG00000025648
<i>6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1</i>	24638	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1	-1.50	0.15	Xq22-q31	ENSRNOG00000000165
<i>Nicotinamide N-methyltransferase</i>	300691	Nicotinamide N-methyltransferase	-1.93	0.25	8q23	ENSRNOG00000005930
<i>NADPH-cytochrome P450 reductase</i>	29441	NADPH-cytochrome P450 reductase	-1.98	0.33	12q12	ENSRNOG00000001442
<i>Aspartate aminotransferase, cytoplasmic</i>	24401	Aspartate aminotransferase, cytoplasmic	-2.14	0.49	1q54	ENSRNOG00000016356
<i>L-serine dehydratase/L-threonine deaminase</i>	25044	L-serine dehydratase/L-threonine deaminase	-6.34	1.56	12	ENSRNOG00000001388
<i>Oxidative stress</i>						
<i>Nuclear factor erythroid 2 related factor 2</i>	83619	Nuclear factor erythroid 2 related factor 2	1.80	0.25	3q23	ENSRNOG0000001548
<i>Peroxiredoxin 1</i>	117254	Peroxiredoxin 1	1.40	0.15	5q36	ENSRNOG00000017194
<i>Glutathione peroxidase 1</i>	24404	Glutathione peroxidase 1	1.21	0.03	16	
<i>KARP-1 binding protein 1</i>	171457	KARP-1 binding protein 1	-1.23	0.05	13q25	ENSRNOG00000004127
<i>Heme oxygenase 1</i>	24451	Heme oxygenase 1	-1.26	0.05	19p11	ENSRNOG00000014117
<i>Sirtuin 4</i>	304539	Sirtuin 4	-1.30	0.08	12q16	ENSRNOG00000001151
<i>Methionine adenosyltransferase I, alpha</i>	25331	Methionine adenosyltransferase I, alpha	-1.54	0.09	16p14	ENSRNOG00000011351
<i>Argininosuccinate synthase</i>	25698	Argininosuccinate synthase	-1.60	0.19	3p12	ENSRNOG00000008837
<i>Tyrosine aminotransferase</i>	24813	Tyrosine aminotransferase	-1.83	0.35	19q11-q12	ENSRNOG00000016348
<i>Transcription</i>						
<i>TSC22 domain family protein 1</i>	498545	TSC22 domain family protein 1	2.47	0.49	15q11	ENSRNOG00000001030

Id2	25587	DNA-binding protein inhibitor ID-2	1.94	0.29	6q16	ENSRNOG00000007237
Zfp347	170902	Gonadotropin inducible ovarian transcription factor 2	1.49	0.19	7q11	ENSRNOG00000031216
VglI2	309772	Vestigial like 2 homolog	1.43	0.13	20q11	ENSRNOG0000000405
Foxa3	25100	Hepatocyte nuclear factor 3-gamma (HNF-3G)	1.41	0.13	1q21-q22	ENSRNOG00000014256
Id4	291023	Inhibitor of DNA binding 4	1.40	0.06	17p14	ENSRNOG00000016099
RGD1564126	291827	Similar to basic transcription factor 3	1.39	0.13	19p14	ENSRNOG00000031076
Trim25	494338	Tripartite motif-containing protein 25	1.34	0.08	10q26	ENSRNOG00000002341
Rnf31	364386	Ring finger protein 31	1.33	0.12	15p13	ENSRNOG00000019438
Hexim1	498008	Hexamethylene bis-acetamide inducible 1	1.30	0.10	10q32.1	ENSRNOG00000003203
Zfp36	79426	Zinc finger protein 36	1.24	0.09	1q21	ENSRNOG00000019673
Larp7	686883	La ribonucleoprotein domain family, member 7	1.24	0.05	2	
Crem	25620	cAMP-responsive element modulator	-2.01	0.34	17q12.1	ENSRNOG00000014900

Ribosomal proteins

RGD1564617	308353	Similar to large subunit ribosomal protein L36a	1.71	0.33	1q21	ENSRNOG00000032062
RGD1564627	502746	Similar to 60S ribosomal protein L38	1.64	0.28	4q22	ENSRNOG00000033808
RGD1565894	291561	Similar to ribosomal protein L31	1.55	0.18	18q12.1	ENSRNOG00000033428
LOC689157	689157	similar to 60S ribosomal protein L23a	1.53	0.20	6q31	
RGD1565806	290916	Similar to 60S ribosomal protein L23a	1.53	0.23	16q12.5	ENSRNOG00000024121
LOC680441	680441	Similar to 60S ribosomal protein L23a	1.48	0.20	4q42	ENSRNOG00000033439
LOC691195	691195	Similar to ribosomal protein L21	1.46	0.20	2q34	
LOC691098	691098	Similar to ribosomal protein L37	1.38	0.15	8q24	ENSRNOG00000034017
RGD1564051	501206	Similar to 60S ribosomal protein L5	1.35	0.10	9q38	ENSRNOG00000037220
LOC686786	686786	60S ribosomal protein L35a	1.33	0.11	7	
RGD1563958	315521	Similar to 60S ribosomal protein L32	1.32	0.11	8q13	ENSRNOG00000028869
RL39	25347	60S ribosomal protein L39	1.30	0.11	Xq12	ENSRNOG00000029751
LOC688948	688948	Similar to ribosomal protein S26	1.29	0.11	5q36	ENSRNOG00000031958
LOC681338	681338	Similar to ribosomal protein L31	1.29	0.09	9q31	ENSRNOG00000032947
LOC680779	680779	Small nuclear ribonucleoprotein polypeptide G	1.28	0.08	14q21	ENSRNOG00000016507
RGD1562937	503183	Similar to ribosomal protein S24	1.21	0.05	8q12	ENSRNOG00000033186

Transporter

Slc34a2	84395	Sodium-dependent phosphate transport protein 2B	1.90	0.25	14q11	ENSRNOG0000004626
Slc28a2	60423	Solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	1.86	0.26	3q35	ENSRNOG00000018204
Slco1b2	58978	Solute carrier organic anion transporter family, member 1b2	1.46	0.14	4q44	ENSRNOG00000030538
Slc16a1	25027	Monocarboxylate transporter 1	1.40	0.08	2q34	ENSRNOG00000019996
Slco1a4	170698	Solute carrier organic anion transporter family, member 1a4	1.33	0.08	4	
Slc16a4	295356	Solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	1.22	0.04	2q34	ENSRNOG00000018131
Mtch2	295922	Mitochondrial carrier homolog 2	-1.21	0.04	3q24	ENSRNOG00000008682
Abcf1	85493	ATP-binding cassette sub-family F member 1	-1.29	0.07	20p12	ENSRNOG0000000799
Slc20a1	81826	Sodium-dependent phosphate transporter 1 (Solute carrier family 20 member 1)	-1.49	0.10	3q36	ENSRNOG00000018567
Slc25a25	246771	Mitochondrial Ca2+-dependent solute carrier	-1.50	0.16	3p11	ENSRNOG00000014338
Slc25a15	306574	Solute carrier family 25 member 15	-1.65	0.30	16q12.5	ENSRNOG00000011881
Slc25a32	315023	Solute carrier family 25, member 32	-1.73	0.26	7q22	ENSRNOG00000004403
Slc38a2	29642	Solute carrier family 38, member 2	-1.79	0.32	7q34	ENSRNOG00000006305
Pxmp4	282634	Peroxisomal membrane protein 4	-2.08	0.19	3q41	ENSRNOG00000016975

Extracellular matrix/Structural proteins

LOC691768	691768	Similar to Thymosin beta-4 (T beta 4)	1.82	0.37	10q23	ENSRNOG00000031043
Lox	24914	Protein-lysine 6-oxidase precursor	1.61	0.30	18q11	ENSRNOG00000014426
Cdh1	83502	Epithelial-cadherin precursor (E-cadherin)	1.50	0.16	19q12	ENSRNOG00000020151
Jup	81679	Junction plakoglobin	1.40	0.16	10q32.1	ENSRNOG00000015380
Mybph	83708	Myosin-binding protein H (MyBP-H) (H-protein)	1.29	0.10	13q13	ENSRNOG0000003336
Actb	81822	Actin, beta	1.25	0.10	12p11	ENSRNOG00000034254
Psen2	81751	Presenilin-2	1.22	0.05	13q26	ENSRNOG00000002879
Sdc1	25216	Syndecan 1	1.22	0.05	6q14	ENSRNOG00000006396
Tpm4	24852	Tropomyosin alpha-4 chain	-1.30	0.10	16p14	ENSRNOG00000015496

Cell cycle & apoptosis

G0s2	289388	G0/G1 switch gene 2	2.68	0.78	13q27	ENSRNOG00000006019
Cdk2ap2	688405	CDK2-associated protein 2	1.42	0.17	1q42	ENSRNOG00000018391
Ethe1	292710	Ethylmalonic encephalopathy 1	1.36	0.13	1q21	ENSRNOG00000019982
Ccnl2	298686	Cyclin-L2	1.34	0.11	5q36	ENSRNOG00000018691
RGD1565371	501140	similar to BCL2/adenovirus E1B 19 kDa-interacting protein 3	-1.35	0.07	9q22	ENSRNOG00000028330

Miscellaneous

LOC680406	680406	similar to Urinary protein 2 precursor (RUP-2)	2.03	0.44	8q21	
LOC367746	367746	Similar to Spindlin-like protein 2 (SPIN-2)	1.64	0.14	Xq13	ENSRNOG00000030868
LOC688253	688253	Similar to Urinary protein 3 precursor (RUP-3)	1.56	0.21	1	
LOC680385	680385	Similar to Sjogren syndrome antigen B	1.54	0.17	4q42	ENSRNOG00000011606
Sgk	29517	Serine/threonine-protein kinase Sgk1	1.49	0.20	1p12	ENSRNOG00000011815
LOC313840	313840	Protein FAM82A	1.49	0.16	6q11	ENSRNOG00000006082
Hfe2	310681	Hemojuvelin precursor (Hemochromatosis type 2 protein homolog)	1.46	0.16	2q34	ENSRNOG00000021200
Cxcl12	24772	Chemokine (C-X-C motif) ligand 12 isoform alpha	1.46	0.10	4q42.1	ENSRNOG00000013589
LOC365231	365231	Similar to heat shock protein 1, alpha	1.42	0.12	1q21	
Palmd	310811	Palmdelphin	1.40	0.13	2q41	
Fam46a	300870	Fam46a family with sequence similarity 46, member A	1.36	0.15	8q31	ENSRNOG00000010240
Oaf	315594	OAF homolog (Drosophila)	1.36	0.16	8q22	ENSRNOG00000009243
Pdia3	29468	Protein disulfide-isomerase A3 precursor	1.35	0.12	3q35	ENSRNOG00000015018

RGD1562723	501932	Similar to Ab2-162	1.34	0.07	14q22	ENSRNOG00000027070
Mreg	501162	Similar to Whn-dependent transcript 2	1.34	0.12	9q33	ENSRNOG00000015774
Ninj1	25338	Ninjurin-1	1.32	0.13	17p14	ENSRNOG00000016587
LOC500300	500300	Protein DEPP	1.32	0.12	4q42	ENSRNOG00000023465
LOC681300	681300	Similar to CXXC finger 5	1.32	0.10	Xq35	ENSRNOG00000003734
Psmc2	25581	26S protease regulatory subunit 7 (MSS1 protein)	1.28	0.08	4q11	ENSRNOG00000012026
Bcar3	310838	Breast cancer anti-estrogen resistance 3	1.28	0.08	2q42	ENSRNOG00000013737
Sfrs18	297942	Splicing factor, arginine/serine-rich 18	1.28	0.12	5q21	ENSRNOG00000008782
Sdf2	287470	Stromal cell derived factor 2	1.28	0.10	10q25	ENSRNOG00000012121
Rab1	81754	RAB1, member RAS oncogene family	1.27	0.06	14q22	ENSRNOG00000004992
Psmc6	289990	Proteasome (prosome, macropain) 26S subunit, ATPase, 6	1.27	0.06	15p14	ENSRNOG00000007203
Nsmce4a	293528	non-SMC element 4 homolog A (S. cerevisiae)	1.26	0.08	1q37	ENSRNOG00000020452
LOC682869	682869	Similar to Golgi phosphoprotein 2 (Golgi membrane protein GP73)	1.26	0.10	17p14	ENSRNOG00000018400
RGD1562407	307029	Similar to WAC	1.25	0.08	17q12.1	ENSRNOG00000018698
Pdlim1	54133	PDZ and LIM domain protein 1 (Elfin)	1.25	0.08	1q53	ENSRNOG00000016166
Hist1h4b	64627	Histone cluster 1, H4b	1.24	0.06	17q11	ENSRNOG00000032366
Uchl3	498560	Ubiquitin carboxyl-terminal esterase L3 (ubiquitin thiolesterase)	1.24	0.05	15q21	ENSRNOG00000006401
Aars	292023	Alanyl-tRNA synthetase	1.24	0.09	19q12	ENSRNOG00000018404
Dusp11	297412	Dual specificity phosphatase 11 (RNA/RNP complex 1-interacting)	1.24	0.05	4q34	ENSRNOG00000022082
Psmb1	94198	Proteasome subunit beta type 1	1.23	0.06	1q12	ENSRNOG00000001488
Mgat2	94273	Mannosyl (alpha-1,6)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase	1.23	0.06	6q24	ENSRNOG00000004234
LOC691877	691877	Similar to suppressor of initiator codon mutations, related sequence 1	1.22	0.07	8q24	ENSRNOG00000029118
RGD1559610	313581	Similar to CGI-94 protein	1.22	0.07	5q36	ENSRNOG00000007174
Tmpo	25359	Thymopoietin	1.22	0.07	7q13	ENSRNOG00000008797
Cwc15	300361	CWC15 homolog (S. cerevisiae)	1.21	0.05	8q11	ENSRNOG00000008490
Dek	306817	DEK oncogene	1.21	0.06	17p13	ENSRNOG00000016152
Oprs1	29336	Opioid receptor, sigma 1	1.21	0.04	5q22	ENSRNOG00000014604
LOC500378	500378	Similar to Protein C1orf77 homolog	1.21	0.05	4	
Stip1	192277	Stress-induced phosphoprotein 1	1.20	0.05	1q43	ENSRNOG00000021164
RGD1561926	500695	Similar to Nuclear protein SkiP (Ski-interacting protein)	1.20	0.05	6q31	ENSRNOG00000037998
Hgd1a	140937	HIG1 domain family member 1A (Hypoxia-inducible gene 1 protein).	-1.20	0.05	8q32	ENSRNOG00000019428
Canx	29144	Calnexin precursor	-1.20	0.04	10q22	ENSRNOG00000003343
RGD1564120	499461	Similar to WNT1 inducible signaling pathway protein 3 precursor (WISP-3)	-1.21	0.03	20q12	ENSRNOG00000000597
Tspan4	293627	Tetraspanin 4	-1.22	0.01	1q41	ENSRNOG00000029810
Cst8	29679	Cystatin-8 precursor	-1.23	0.04	3q41	ENSRNOG00000004989
Pfdn6	309629	Prefoldin 6	-1.23	0.04	20p12	ENSRNOG00000000473
Enth	360515	Enthoprotin	-1.24	0.04	10q21	ENSRNOG00000005406
Anpep	81641	Aminopeptidase N	-1.25	0.07	1q31	ENSRNOG00000014610
Dlgap1	65040	Disks large-associated protein 1	-1.25	0.08	9q38	ENSRNOG00000016196
Lrpprc	313867	Leucine-rich PPR motif-containing protein, mitochondrial precursor	-1.26	0.03	6q12	ENSRNOG00000005877
Il1rn	60582	Interleukin-1 receptor antagonist protein precursor	-1.26	0.09	3p13	ENSRNOG00000005871
Nup155	117021	Nuclear pore complex protein Nup155	-1.27	0.08	2q16	ENSRNOG00000013411
Nup37	299706	Nucleoporin 37	-1.28	0.07	7q13	ENSRNOG00000004727
Creg1	289185	Cellular repressor of E1A-stimulated genes	-1.30	0.04	13q23	ENSRNOG00000003291
Btd	306262	Biotinidase precursor	-1.33	0.03	16p16	ENSRNOG00000019656
Ptpn2	117063	Tyrosine-protein phosphatase non-receptor type 2	-1.34	0.09	18q12.1	ENSRNOG00000017453
LOC679748	679748	Similar to Macrophage migration inhibitory factor	-1.35	0.16	1q21	ENSRNOG00000034106
RGD1560263	499670	Similar to nuclear receptor binding factor 2	-1.36	0.08	2q34	ENSRNOG00000030494
Rarres1	310486	Retinoic acid receptor responder (tazarotene induced) 1	-1.36	0.08	2q31	ENSRNOG00000037853
Sh3bp5	117186	SH3 domain-binding protein 5 (Vascular endothelial cell-specific protein 18).	-1.39	0.11	16p16	ENSRNOG00000019475
Agt	24179	Angiotensinogen precursor (Serpin A8)	-1.44	0.11	19q12	ENSRNOG00000018445
Birc2	60371	Baculoviral IAP repeat-containing 2	-1.44	0.14	8q11	ENSRNOG00000010602
Gnl3	290556	Guanine nucleotide binding protein-like 3 (Nucleolar GTP-binding protein 3)	-1.49	0.19	16p16	ENSRNOG00000028461
Fam89a	361441	Family with sequence similarity 89, member A	-1.49	0.07	19q12	ENSRNOG00000019022
Rgs3	54293	Regulator of G-protein signaling 3	-1.52	0.18	5q24	ENSRNOG00000024501
Usp11	288447	Ubiquitin specific peptidase like 1	-1.53	0.19	12p11	ENSRNOG0000000909
Sdc4	24771	Syndecan-4 precursor (Ryudocan core protein)	-1.55	0.18	3q42	ENSRNOG00000014297
Arsb	25227	Arylsulfatase B	-1.55	0.14	2q12	ENSRNOG00000011150
Sat	302642	Spermidine/spermine N1-acetyl transferase	-1.62	0.20	Xq22	ENSRNOG00000003809
Xbp1	289754	X-box binding protein 1	-1.69	0.23	14q21	ENSRNOG00000010298
Dpt	289178	Dermatopontin precursor	-1.80	0.27	13q23	ENSRNOG00000002947
Ankhd1	679725	Ankhd1-Eif4ebp3 fusion transcript	-2.08	0.39	18p11	ENSRNOG00000030247
Gadd45a	25112	Growth arrest and DNA-damage-inducible protein GADD45 alpha	-2.41	0.54	4q31-43	ENSRNOG00000005615
Hhex	79237	Hematopoietically expressed homeobox	-2.84	0.65	1q53	ENSRNOG00000016595
Coq10b	301416	Coenzyme Q10 homolog B (S. cerevisiae)	-2.94	0.94	9q31	ENSRNOG00000014456
Rup2	619560	Urinary protein 2	-3.31	0.97	8q21	ENSRNOG00000028823

Unknown function and hypothetical proteins

RGD1308116	310376	Similar to RIKEN cDNA E130304F04 gene	1.58	0.18	2q16	ENSRNOG00000016353
RGD1564945	366248	Hypothetical gene supported by NM_053330	1.42	0.19	3q42	ENSRNOG00000033586
RGD1309308	313115	Similar to RIKEN cDNA 1810074P20	1.30	0.09	5q21	ENSRNOG00000007831
RGD1309735	360776	Similar to CG14977-PA	-1.20	0.05	12q11	ENSRNOG00000027028
LOC502374	502374	Hypothetical protein LOC502374	-1.24	0.07	1q41	ENSRNOG00000019293
RGD1309676	361118	Uncharacterized protein C10orf58 homolog precursor	-1.24	0.05	16p14	ENSRNOG00000011140
RGD1559628	501945	Similar to RIKEN cDNA 1110003E01	-1.28	0.08	15p16	ENSRNOG00000031985
RGD1311122	364154	Similar to RIKEN cDNA 1110003E01	-1.31	0.07	14p11	ENSRNOG00000002553
LOC679527	679527	Similar to RIKEN cDNA 1110003E01	-1.32	0.07	15p16	ENSRNOG00000028863
LOC360692	360692	PREDICTED: similar to DNA segment, Chr 16, ERATO Doi 472, expressed	-1.90	0.43	11q11	ENSRNOG00000001554

Supplemental Material, Table 4. Regulated pathways in liver of rats fed HFC compared to HFR.

Up-regulated pathways						
NAME	SIZE	ES	NES	NOM p-val	FDR q-val	FWER p-val
HSA05131_PATHOGENIC_ESCHERICHIA_COLI_INFECTION_EPEC	30	0.685	2.278	0	0.002	0.002
HSA05130_PATHOGENIC_ESCHERICHIA_COLI_INFECTION_EHEC	30	0.685	2.234	0	0.001	0.002
HSA03050_PROTEASOME	20	0.699	2.044	0	0.029	0.081
MMS_HUMAN_LYMPH_LOW_4HRS_DN	12	0.747	1.944	0	0.100	0.330
BHATTACHARYA_ESC_UP	37	0.570	1.927	0	0.100	0.398
MAGRANGEAS_MULTIPLE_MYELOMA_IGL_VS_IGK_UP	9	0.790	1.889	0.002	0.139	0.581
PROTEASOME_DEGRADATION	23	0.613	1.876	0	0.141	0.631
TGFBETA_C2_UP	14	0.684	1.840	0	0.196	0.795
EMT_DN	45	0.509	1.831	0.004	0.191	0.830
LVAD_HEARTFAILURE_DN	29	0.567	1.823	0.002	0.191	0.858
CITED1_KO_HET_UP	19	0.622	1.805	0.004	0.215	0.911
DER_IFNA_UP	44	0.505	1.801	0.004	0.207	0.920
OLDONLY_FIBRO_DN	36	0.523	1.786	0	0.226	0.950
DFOSB_BRAIN_8WKS_UP	34	0.522	1.778	0.004	0.230	0.961
HSA00072_SYNTHESIS_AND_DEGRADATION_OF_KETONE_BODIES	7	0.819	1.776	0.006	0.218	0.964
HSA00100 BIOSYNTHESIS_OF_STEROIDS	18	0.615	1.770	0.010	0.220	0.971
Down-regulated pathways						
NAME	SIZE	ES	NES	NOM p-val	FDR q-val	FWER p-val
HSA00272_CYSTEINE_METABOLISM	12	-0.821	-2.084	0	0.066	0.065
HSA00330ARGININE_AND_PROLINE_METABOLISM	27	-0.647	-2.077	0	0.042	0.083
HTERT_DN	49	-0.557	-2.007	0	0.078	0.217
HSA00220UREA_CYCLE_AND_METABOLISM_OF_AMINO_GROUPS	23	-0.667	-1.991	0	0.071	0.256
HYPOXIA REVIEW	60	-0.537	-1.989	0	0.059	0.263
HSA00400PHENYLALANINE_TYROSINE_AND_TRPTOPHAN BIOSYNTHESIS	9	-0.844	-1.988	0.002	0.050	0.267
GLUTAMATE_METABOLISM	16	-0.737	-1.973	0	0.054	0.321
WERNERONLY_FIBRO_DN	44	-0.550	-1.925	0	0.088	0.499
ARGININE_AND_PROLINE_METABOLISM	28	-0.619	-1.921	0	0.081	0.508
HIF1 TARGETS	25	-0.627	-1.916	0.002	0.078	0.526
UREACYCLEPATHWAY	5	-0.972	-1.911	0	0.075	0.550
FETAL_LIVER_VS_ADULT_LIVER_GNF2	46	-0.544	-1.905	0	0.075	0.586
CARDIACEGFPATHWAY	13	-0.726	-1.898	0	0.077	0.638
BUT_TSA_UP	16	-0.692	-1.892	0.002	0.077	0.669
HSA00251GLUTAMATE_METABOLISM	20	-0.643	-1.861	0.006	0.106	0.810
DREAMPATHWAY	10	-0.777	-1.859	0.004	0.102	0.819
PHENYLALANINE_TYROSINE_AND_TRPTOPHAN BIOSYNTHESIS	8	-0.821	-1.842	0	0.122	0.884
UVC_HIGH_ALL_UP	14	-0.686	-1.822	0.004	0.145	0.920
CMV_HCMV_TIMECOURSE_6HRS_DN	38	-0.533	-1.797	0	0.180	0.969
CYSTEINE_METABOLISM	8	-0.812	-1.790	0.002	0.185	0.975
TNFA_NFKB_DEP_UP	12	-0.683	-1.763	0.010	0.231	0.990
HSA00252ALANINE_AND ASPARTATE_METABOLISM	30	-0.547	-1.754	0.012	0.240	0.992

Supplemental Material, Table 5. Storage of organic pollutants in insulin sensitive tissues of rats fed HFC.

Persistent organic pollutants (weight/g tissue)	Liver	Adipose tissue	Skeletal muscle
Organochlorine pesticides, ng/g			
Alpha-hexachlorocyclohexane	<LOQ	<LOQ	<LOQ
Gamma-hexachlorocyclohexane	<LOQ	<LOQ	<LOQ
Hexachlorobenzene	0.71 ± 0.13	6.42 ± 0.24	<LOQ
Heptachlor	<LOQ	<LOQ	<LOQ
Heptachlor endo-epoxide	<LOQ	<LOQ	<LOQ
Oxychlordane	<LOQ	1.84 ± 0.06	<LOQ
Trans-chlordane	<LOQ	<LOQ	<LOQ
Cis-chlordane	<LOQ	<LOQ	<LOQ
Aldrin	<LOQ	<LOQ	<LOQ
Alpha-endosulfan	<LOQ	<LOQ	<LOQ
Beta-endosulfan	<LOQ	<LOQ	<LOQ
Endosulfan-sulfate	<LOQ	<LOQ	<LOQ
Trans-nonachlor	<LOQ	<LOQ	<LOQ
Cis-nonachlor	<LOQ	<LOQ	<LOQ
Toxaphene-26	<LOQ	<LOQ	<LOQ
Toxaphene-32	<LOQ	<LOQ	<LOQ
Toxaphene-50	<LOQ	<LOQ	<LOQ
Toxaphene-62	<LOQ	<LOQ	<LOQ
Dichloro-diphenyl-trichloroethanes (DDTs), ng/g			
op'-DDT	<LOQ	0.41 ± 0.04	<LOQ
pp'-DDT	<LOQ	4.70 ± 0.68	<LOQ
op'-DDD	<LOQ	0.29 ± 0.03	<LOQ
pp'-DDD	<LOQ	6.54 ± 0.69	<LOQ
op'-DDE	0.29 ± 0.02	0.73 ± 0.13	<LOQ
pp'-DDE	18.54 ± 2.04	23.82 ± 1.67	<LOQ
Polychlorinated dibenzo-p-dioxins (PCDDs), pg/g			
2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)	ND	ND	NA
1,2,3,7,8-Pentachlorodibenzodioxin (1,2,3,7,8-PeCDD)	ND	<LOQ	NA
1,2,3,4,7,8-Hexachlorodibenzodioxin (1,2,3,4,7,8-HxCDD)	ND	ND	NA
1,2,3,6,7,8-Hexachlorodibenzodioxin (1,2,3,6,7,8-HxCDD)	0.52 ± 0.03	ND	NA
1,2,3,7,8,9-Hexachlorodibenzodioxin (1,2,3,7,8,9-HxCDD)	ND	ND	NA
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (1,2,3,4,6,7,8-HpCDD)	1.04 ± 0.16	<LOQ	NA
Octachlorodibenzodioxin (OCDD)	2.94 ± 0.56	ND	NA
Polychlorinated dibenzofurans (PCDFs), pg/g			
2,3,7,8-Tetrachlorodibenzofuran (2,3,7,8-TCDF)	1.30 ± 0.19	2.25 ± 0.11	NA
1,2,3,7,8-Pentachlorodibenzofuran (1,2,3,7,8-PeCDF)	ND	ND	NA
2,3,4,7,8-Pentachlorodibenzofuran (2,3,4,7,8-PeCDF)	2.66 ± 0.40	<LOQ	NA
1,2,3,4,7,8-Hexachlorodibenzofuran (1,2,3,4,7,8-HxCDF)	<LOQ	ND	NA
1,2,3,6,7,8-Hexachlorodibenzofuran (1,2,3,6,7,8-HxCDF)	<LOQ	ND	NA
1,2,3,7,8,9-Hexachlorodibenzofuran (1,2,3,7,8,9-HxCDF)	ND	ND	NA
2,3,4,6,7,8-Hexachlorodibenzofuran (2,3,4,6,7,8-HxCDF)	<LOQ	ND	NA
1,2,3,4,6,7,8-Heptachlorodibenzofuran (1,2,3,4,6,7,8-HpCDF)	0.38 ± 0.04	ND	NA
1,2,3,4,7,8,9-Heptachlorodibenzofuran (1,2,3,4,7,8,9-HpCDF)	ND	ND	NA
Octachlorodibenzofuran (OCDF)	ND	ND	NA
Non-ortho-substituted PCBs, pg/g			
3,3',4,4'- Tetrachlorobiphenyl (CB-77)	<LOQ	17.77 ± 0.58	NA
3,4,4',5- Tetrachlorobiphenyl (CB-81)	ND	<LOQ	NA
3,3',4,4',5- Pentachlorobiphenyl (CB-126)	12.73 ± 1.89	24.77 ± 1.34	NA

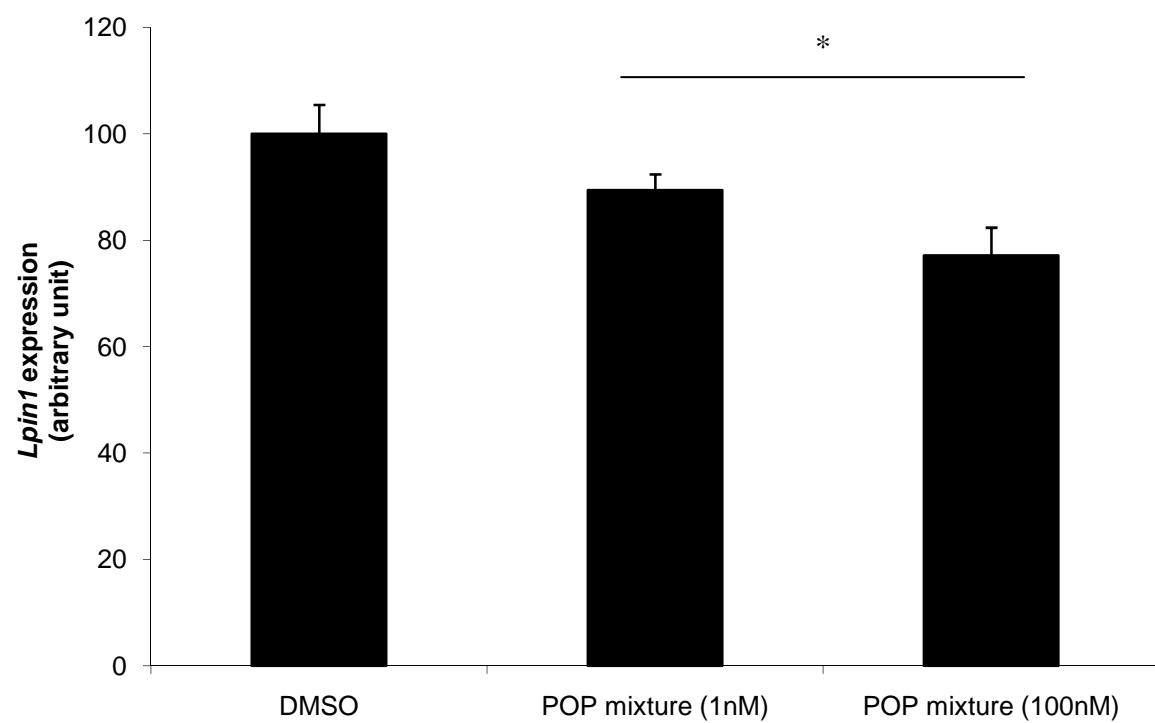
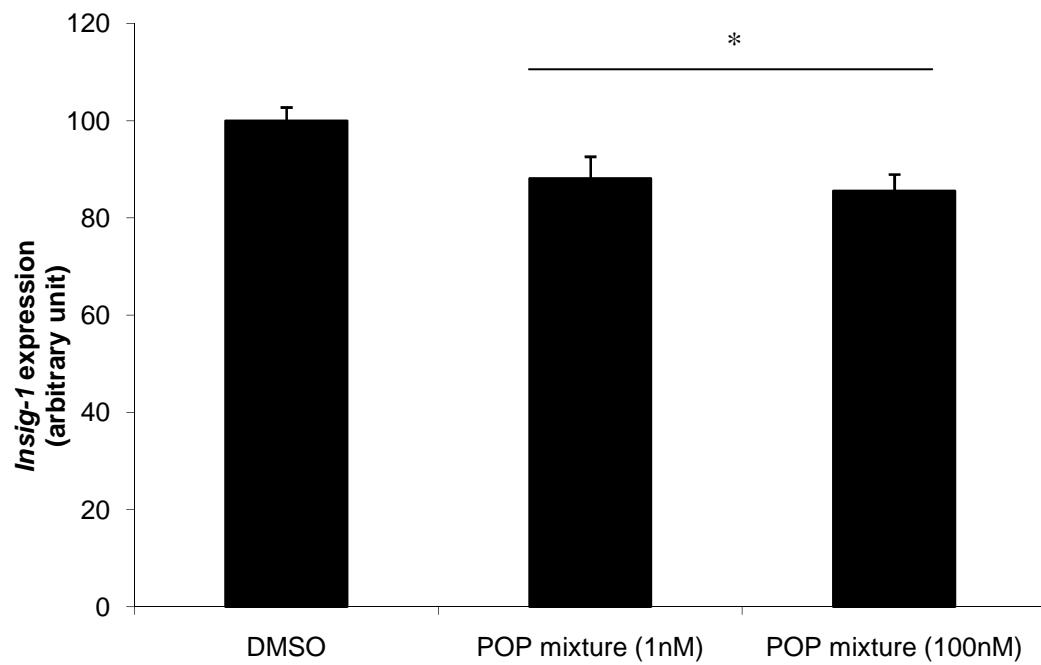
3,3',4,4',5,5'- Hexachlorobiphenyl (CB-169)	2.66 ± 0.21	<LOQ	NA
Mono-ortho-substituted PCBs, pg/g			
2,3,3',4,4'- Pentachlorobiphenyl (CB-105)	224.24 ± 16.17	1756.26 ± 97.50	NA
2,3,4,4',5- Pentachlorobiphenyl (CB 114)	<LOQ	<LOQ	NA
2,3',4,4',5- Pentachlorobiphenyl (CB-118)	660.30 ± 55.39	5072.32 ± 288.65	NA
2',3,4,4',5- Pentachlorobiphenyl (CB-123)	<LOQ	90.18 ± 6.03	NA
2,3,3',4,4',5- Hexachlorobiphenyl (CB-156)	79.36 ± 6.78	490.50 ± 60.54	NA
2,3,3',4,4',5'- Hexachlorobiphenyl (CB-157)	<LOQ	135.88 ± 7.48	NA
2,3',4,4',5,5'- Hexachlorobiphenyl (CB-167)	53.02 ± 4.01	300.34 ± 18.33	NA
2,3,3',4,4',5,5'- Heptachlorobiphenyl (CB-189)	12.10 ± 1.28	41.24 ± 3.41	NA
Polychlorinated biphenyls (PCBs), ng/g			
2,4,4'-Trichlorobiphenyl (CB-28)	0.12 ± 0.01	1.15 ± 0.05	NA
2,2',5,5'-Tetrachlorobiphenyl (CB-52)	<LOQ	0.24 ± 0.02	NA
2,2',4,5,5'-Pentachlorobiphenyl (CB-101)	0.30 ± 0.02	3.46 ± 0.04	NA
2,3',4,4',5-Pentachlorobiphenyl (CB-118)	0.66 ± 0.06	5.07 ± 0.29	NA
2,2',3,4,4',5'-Hexachlorobiphenyl (CB-138)	1.80 ± 0.16	12.33 ± 0.76	NA
2,2',4,4',5,5'-Hexachlorobiphenyl (CB-153)	1.72 ± 0.19	12.08 ± 0.51	NA
2,2',3,4,4',5,5'-Heptachlorobiphenyl (CB-180)	0.55 ± 0.04	2.55 ± 0.15	NA

ND, not detected; NA, not analyzed; < LOQ, below limit of quantification.

Supplemental Material, Figure 1. Effect of POPs on *Insig-1* and *Lipin1* mRNA expression.

Differentiated 3T3-L1 adipocytes were treated without (DMSO) or with POP mixture at indicated concentrations for 48 hours and mRNA expression of *Insig-1* and *Lipin1* were assessed by real-time PCR. Data are presented as means \pm SEM, $n = 9$, * Significantly different ($P < 0.02$).

Supplemental Material, Figure 1. Effect of POPs on *Insig-1* and *lpin1* mRNA expression.



Supplemental Material, Figure 2. Measurement of lactate dehydrogenase levels.

Levels of lactate dehydrogenase (LDH) in supernatants of cultured adipocytes exposed to POP mixtures were determined and compared to positive control (0.1% triton X-100)-treated cells. Data are presented as means \pm SEM, $n = 7-8$. * $P < 0.0001$ vs. triton X-100-treated cells.

Supplemental Material, Figure 2. Measurement of lactate dehydrogenase levels.

